Vasoconstrictor Agents for Local Anesthesia

John A. Yagiela, DDS, PhD

Section of Oral Biology, School of Dentistry, University of California, Los Angeles, Los Angeles, California

One hundred years ago, the English physician George Oliver reported that extracts of the adrenal gland exerted powerful effects on the heart and blood vessels.[1] Several years later, the American pharmacologist John Abel isolated the active principal, naming it epinephrine. In 1900 a Japanese industrial chemist, Jokichi Takamine, discovered how to obtain epinephrine in pure form and arranged for the drug to be marketed by Park, Davis, and Company of the United States under the trade name of "Adrenaline," which subsequently became the official name of the hormone in most other countries. The use of epinephrine to enhance local anesthesia was conceived by Heinreich Braun, a noted German authority on nerve blockade. In 1904, Braun combined epinephrine with procaine. The resultant local anesthetic preparation, Novocain with Adrenalin, marketed by the Hoechst Company, went on to dominate the field for nearly a half century.

In subsequent years, nordefrin, phenylephrine, norepinephrine, and levonordefrin were developed as adrenergic vasoconstrictors. None of these agents has proved superior or perhaps even equal to epinephrine, and only norepinephrine and levonordefrin are still used. Felypressin, a derivative of the antidiuretic hormone vasopressin, was introduced as an alternative to adrenergic vasoconstrictors. Lacking the hemostatic potential of epinephrine, felypressin is best reserved for selected clinical situations. In the review that follows, I will therefore concentrate on epinephrine, discussing these other drugs only as they compare to it.

MECHANISM OF ACTION

Epinephrine and related adrenergic amines cause vasoconstriction by stimulating specific membrane-bound receptors on vascular smooth muscle cells. Two major types of adrenergic receptors, termed α_1 and α_2, can initiate vasoconstriction. Anatomically, the α_1 receptor is located adjacent to sympathetic nerves innervating blood vessels, whereas the α_2 receptor is distributed such that it is more likely to respond to circulating catecholamines. Epinephrine injected into peripheral tissues stimulates both receptors.

In recent years, the cascade of events leading from receptor stimulation to vasoconstriction has been elucidated.[2] Adrenergic receptors are linked to effector enzymes and ion channels by what are called "G" proteins, polypeptides that bind guanosine triphosphate when adrenergic receptors are stimulated by epinephrine (Figure 1). Activation of G proteins linked to α_1 receptors results in the opening of plasma membrane calcium channels and stimulation of the enzyme phospholipase C. Calcium ions flow into the cell and activate calmodulin-dependent myosin light chain kinase, which in turn initiates muscle contraction. Meanwhile, hydrolysis by phospholipase C of the membrane constituent phosphatidylinositol biphosphate leads to the formation of inositol triphosphate and diacylglycerol. These so-called second messengers promote contraction by facilitating the release of calcium from intracellular stores and by fostering activation of protein kinase C, which helps to provide metabolic support for contraction. Vasoconstrictor stimulation of α_2 receptors also opens calcium channels through activation of G proteins. In addition, the enzyme adenylate cyclase is inhibited by way of an inhibitory G protein, G_i. Adrenergic receptors, termed β_2, activate adenylate cyclase and cause vasodilation. Prevalent in blood vessels supplying skeletal muscle and certain viscera, β_2 receptors are relatively uncommon in mucous membranes and skin.

Norepinephrine shares with epinephrine the ability to activate both α_1 and α_2 receptors. Because it does not interact with β_2 receptors, however, norepinephrine's only direct effect on the vasculature is to promote constriction. Levonordefrin is even more restricted in scope, selectively activating α_2 vascular receptors. Felypressin causes vasoconstriction by binding to the vasopressin V_1 receptor. The V_1 receptor is linked to phospholipase C and produces effects as outlined above.

CONSEQUENCES OF LOCAL VASOCONSTRICTION

Epinephrine-induced vasoconstriction can strongly influence the duration and even the intensity of nerve blockade by local anesthetics. In opposing the vasodilating action of the local anesthetic, epinephrine retards its absorption from the injection site. This delay permits the

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Address correspondence to Dr. John Yagiela, UCLA School of Dentistry, Center for the Health Sciences, Los Angeles, CA 90095.

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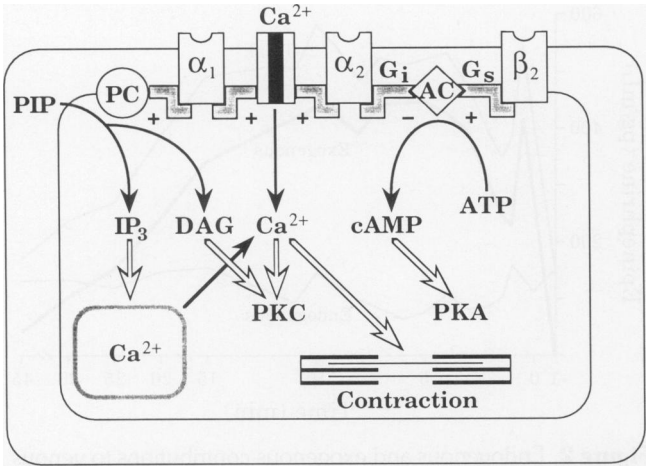

Figure 1. Intracellular responses to receptor binding. Adrenergic receptors directly influencing vascular tone are coupled via guanine nucleotide-binding proteins (G_s, G_i, and unlabeled shaded connectors) to effector proteins: adenylate cyclase (AC), phospholipase C (PC), and calcium (Ca^{2+}) channels. Signal transduction by effector proteins (shown in black arrows) results in altered concentrations of second messengers: cyclic adenosine monophosphate (cAMP), Ca^{2+}, inositol-1,4,5-triphosphate (IP_3), and diacylglycerol (DAG). The second messengers in turn activate (white arrows) various enzymes, such as protein kinase A (PKA) and protein kinase C (PKC), and cause ionic fluxes (such as release of Ca^{2+} from intracellular storage sites). Increased Ca^{2+} activates muscle contraction and vasoconstriction. (From Jastak JT, Yagiela JA, Donaldson D: Local Anesthesia of the Oral Cavity. Philadelphia, WB Saunders Co., 1995.)

local anesthetic to reach its site of action within the nerve membrane in sufficient concentrations to provide an extended duration of action. The actual prolongation of anesthesia obtained varies with the local anesthetic, its concentration, the type and concentration of the vasoconstrictor, and the site of injection. Thus, the duration of mandibular anesthesia caused by 4% prilocaine is little influenced by 1:200,000 epinephrine whereas the that of 2% lidocaine is markedly increased.[3,4] In the case of lidocaine and other strong vasodilators injected into highly vascular oral tissues, the coadministration of epinephrine may be a prerequisite for achieving clinical anesthesia. The landmark studies of Björn and Huldt[5] demonstrated this point when they showed that 1% lidocaine was completely ineffective after maxillary infiltration but highly effective when administered with epinephrine. Indeed, the addition of 1:100,000 epinephrine increased the anesthetic efficiency of 1% lidocaine to beyond that achieved by 4% lidocaine without vasoconstrictor.

These beneficial effects of the vasoconstrictor may persist long after it has been removed from the local tissues, a process that usually takes from 30 min to 1 hr. With bupivacaine, for example, Trieger and Gillen[6] found that the addition of epinephrine increased the duration of anesthesia from 5.8 to 7.0 hr. Once additional bupivacaine is allowed by epinephrine to reach the nerve membrane, instead of being absorbed into the systemic circulation, the drug's extreme lipid solubility permits it to remain there for an extended period of time.

Local hemostasis is often a desired effect during surgical procedures. Inasmuch as local anesthetic solutions with vasoconstrictors are generally used for convenience, as well as to provide supplemental pain relief, the net effect achieved is influenced by the vasodilating potential of the local anesthetic. With lidocaine, a clear dose response for epinephrine has been demonstrated, with 1:50,000 epinephrine being more effective than less concentrated solutions.[7] Although 1:200,000 epinephrine seems to provide adequate hemostasis when coupled with 4% prilocaine or 0.5% bupivacaine, it is insufficient when added to 1.5% etidocaine. Because felypressin appears to act preferentially on the venous microcirculation, it is not effective as a hemostatic agent for surgery.

One concern regarding vasoconstriction is its possible effect on the supply of nutrients to, and the removal of waste products from, local tissues. Liabilities demonstrated in humans include increased postoperative bleeding and pain and delayed wound healing. Studies in animals have documented that pulpal blood flow is acutely depressed by adrenergic vasoconstrictors. For example, Kim[8] recorded in dogs a 70% reduction in pulpal blood flow 5 min after infiltration of 2% lidocaine with 1:100,000 epinephrine over the maxillary canine. With certain injections, such as periodontal ligament injection of the mandibular premolar, pulpal blood flow may be completely blocked for up to 30 min. The short- and long-term effects this may have on pulpal health have not been explored.

A consequence of the retarded absorption rate is often a reduced peak blood concentration of local anesthetic. As derived from data published by Cannell et al,[9] the maximum blood concentration of lidocaine is reduced by approximately 40% when the drug is administered with 1:80,000 epinephrine. By permitting metabolism of the local anesthetic to keep pace with systemic absorption, it is logical to assume that systemic toxic effects may be reduced. This supposition is based, however, on two assumptions: (1) vasoconstrictors have no influence on local anesthetic toxicity other than their ability to retard systemic absorption, and (2) vasoconstrictors are themselves without toxic liabilities when used as adjuvants for dental anesthesia. With regard to the first assumption, studies in rodents suggest that local anesthetic lethality can be increased by vasoconstrictors. In rats, the median intravenous lethal dose of 2% lidocaine is about 28 mg/kg.[10] When combined with 1:100,000 epinephrine, the median lethal dose falls to about 18 mg/kg. As indicated by physiologic tracings of electroencephalographic, elec-

trocardiographic, respiratory, and arterial pressure responses, rats die from central nervous system depression and cessation of respiration; blood pressure is maintained until cardiovascular system function becomes disrupted by hypoxia.[11] Measurements of cardiac output and regional blood flow indicate that epinephrine redirects a larger than normal percentage of the cardiac output to the brain, compensating for the decrease in cardiac output caused by the lidocaine. The net effect is maintenance of cerebral blood flow at the expense of other tissues, and a doubling of the delivery of lidocaine to the brain. It is not known whether a similar chain of events can occur in humans. The second assumption, that vasoconstrictors are themselves without toxic liabilities when used as adjuvants for dental anesthesia, is best reviewed by a consideration of the systemic effects of vasoconstrictors.

SYSTEMIC EFFECTS

A source of enduring controversy in dentistry is the potential of epinephrine for causing systemic effects when used in small amounts during local anesthesia. Historically, pronouncements of grave risk have clashed with deprecations of any danger. The intensity of such debates were fueled for many years by the unavailability of vasoconstrictor-free local anesthetics effective for pulpal anesthesia.

It is now an established fact that the epinephrine injected during routine dental anesthesia significantly elevates the plasma concentration of the hormone. According to a meta-analysis[12] of various studies, a single cartridge of 2% lidocaine with 1:100,000 epinephrine, equivalent to 18 μg of the vasoconstrictor, can be expected to double the resting epinephrine concentration. Concentrations achieved with multiple injections may approximate those associated with such stresses as acute myocardial infarction, strenuous exercise, and insulin-induced hypoglycemia.[13] The most direct demonstration that the elevated epinephrine is due to the exogenous drug and not to epinephrine released from the adrenal gland was provided by Lipp et al,[14] who injected articaine with radiolabeled epinephrine before periodontal therapy (Figure 2). Virtually all of the epinephrine increase was exogenous in origin. The early spike at 30 sec reflects abrupt, massive increases of epinephrine in four of 20 subjects, presumably from intravascular injection; the smaller peak at 10 min marks the beginning of deep scaling.

Despite these markedly elevated concentrations, cardiovascular responses to injected epinephrine are usually modest. As originally described for brachial plexus block by Kennedy et al,[15] and subsequently verified after intraoral injections by others, heart rate and mean blood

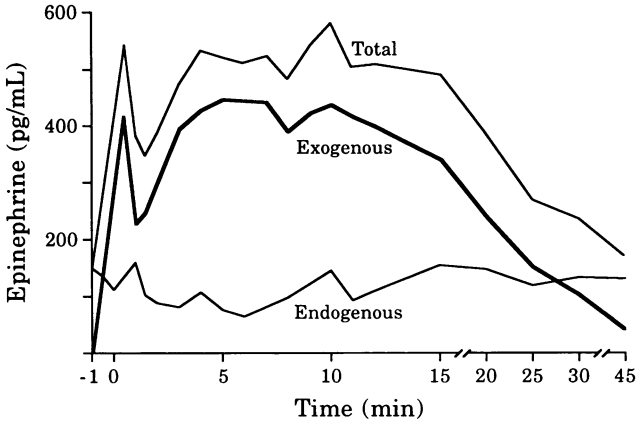

Figure 2. Endogenous and exogenous contributions to venous plasma epinephrine after the injection of 2 mL of 4% articaine with 1:100,000 [^{3}H]epinephrine. The early spike at 30 sec reflects abrupt, massive increases of exogenous epinephrine in four of the 20 subjects; the smaller peak at 10 min marks the beginning of dental treatment (deep scaling). (Data from Lipp et al[14]; drawing from Jastak JT, Yagiela JA, Donaldson D: Local Anesthesia of the Oral Cavity. Philadelphia, WB Saunders Co., 1995.)

pressure are often not significantly affected, a reflection of the body's capacity for homeostatic regulation. Cardiac output is uniformly increased, but only in the 20% to 50% range with dosages of epinephrine normally used in dentistry. A parallel decrease in peripheral vascular resistance, reflecting systemic β_2-receptor activation by epinephrine, helps preclude hypertensive responses.

It is clear from these data that epinephrine does not usually elicit dramatic systemic cardiovascular responses. Simply, elevating plasma epinephrine is not identical to increasing sympathetic tone. With sympathetic arousal, adrenergic neurons release norepinephrine at neuroeffector synapses to increase the rate and force of contraction and to redirect blood away from mucosa, skin, and most viscera. The primary cardiovascular roles of epinephrine released during sympathetic nervous system stimulation are to cause vasodilation in skeletal muscle and to assist return of blood to the heart by constricting capacitance veins in the legs and abdomen. In addition, epinephrine is primarily responsible for bronchodilation and for the metabolic changes that accompany sympathetic discharge; these include elevated plasma glucose, increased lipolysis, and decreased plasma potassium.

Systemic effects of vasoconstrictor alternatives to epinephrine are qualitatively different, at least in usual doses. Because of their relative inability to stimulate vasodilator β_2 receptors, norepinephrine and levonordefrin do not reduce peripheral resistance. Arterial blood pressure is more likely to rise instead of cardiac output, and reflex bradycardia is more likely than tachycardia. Felypressin has little or no direct effect on the myocardium

and causes few systemic cardiovascular effects in conventional doses.

ADVERSE REACTIONS

Although systemic responses to vasoconstrictors in local anesthetic solutions are generally mild, adverse reactions may occur in certain situations. Patients with heart disease are the largest group at risk and will serve as the focus for the remainder of this presentation. Specific dangers to cardiac patients include myocardial ischemia and dysrhythmia. Measures of cardiac performance, such as cardiac output, left ventricular ejection fraction, and myocardial contractility index, are less influenced by epinephrine in patients with coronary artery disease than in normal subjects. This insensitivity may reflect reduced cardiac reserve or a down regulation of cardiac β receptors. Nevertheless, myocardial oxygen consumption, which goes up in response to the increased cardiac work, begins to outpace oxygen delivery in patients with coronary artery disease as the epinephrine infusion rate approaches 0.06 μg/kg/min. In one study, clinically evident myocardial ischemia occurred in sensitive patients when the epinephrine concentration exceeded 650 pg/mL.[16] Signs and symptoms of ischemia included chest pain, ST-segment depression, and ventricular dysrhythmias.

Norepinephrine and levonordefrin are not preferred over epinephrine for patients with heart disease. Although patients may complain less of palpitation, because these drugs tend to cause reflex vagal activity and slowing of the heart rate, they have at least the same potential for impairing myocardial oxygenation and causing ventricular dysrhythmias. In addition, they can place more stress on the heart than epinephrine because of their tendency to increase peripheral resistance and cardiac afterload. Felypressin is a good substitute for patients with dysrhythmia; its tendency to constrict coronary blood vessels makes its use in patients with angina pectoris less advantageous.

Adverse responses to vasoconstrictors are magnified when the drug gains quick access to the blood stream. Intravascular injections of 15 to 20 μg epinephrine uniformly and significantly increase heart rate. Careful aspiration is therefore a prerequisite when administering vasoconstrictors to heart patients. Since rapid entry of drug into the vascular compartment may occur despite negative aspiration attempts, each cartridge should be administered slowly. Inasmuch as intraosseous and periodontal ligament injections may lead to rapid vasoconstrictor uptake, their use is problematic in cardiac patients.

Finally, there is the question of dose. Virtually all of the adverse effects associated with vasoconstrictors are dose dependent. Though various authorities have recommended specific amounts of epinephrine—from nothing to 0.2 mg—for patients with cardiovascular disease, there is no single standard that can apply to all patients and clinical situations. Some patients with well-controlled disorders may be treated appropriately without specific modification. At the other extreme, a patient with unstable angina and poorly controlled ventricular dysrhythmia may not be a candidate for any epinephrine (assuming the patient requires emergency treatment under local anesthesia). A total limit of 40 μg may be appropriate for the cardiac patient with stable angina pectoris and ability to climb a single flight of stairs without difficulty. Perhaps the recommendation offered in 1986 by the American Heart Association[17] is as good as any summary pronouncement on this subject: "Vasoconstrictor agents should be used in local anesthesia solutions during dental practice only when it is clear that the procedure will be shortened or the analgesia rendered more profound. When a vasoconstrictor is indicated, extreme care should be taken to avoid intravascular injection. The minimum possible amount of vasoconstrictor should be used."

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